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human reproduction LETTER TO THE EDITOR

Is the association of replete status in vitamin D with better results in IVF demonstrated?

Sir,

We read with attention the interesting article 'Vitamin D and assisted reproductive treatment outcomes: a systematic review and meta-analysis' (Chu *et al.*, 2018), since we are performing a similar work (Iliuta, 2018). After a thorough review of their data, we found some apparent mistakes in the data retrieval from the references and in the data classification process. Reanalysis of corrected data leads, in our view, to different results and inferences not in agreement with those proposed in the paper.

The authors reviewed 11 publications, including 2700 participants and compared vitamin D replete women to those with deficient or insufficient vitamin D status. It was concluded that replete vitamin D women were more likely to achieve pregnancy (OR 1.34 [1.04–1.73]), clinical pregnancy (OR 1.46 [1.05–2.02]) and live birth (OR 1.33 [1.08–1.65]) than vitamin D deficient and insufficient women.

One of the six included studies for the live birth calculation (Polyzos *et al.*, 2014) was reported as having 61 events out of 129 replete women vs 139 in 368 'deficient and insufficient women'. However, (Polyzos *et al.*, 2014) original manuscript presents a live birth rate of 61/129 for the 'replete and insufficient' group and 78/239 for the deficient group. Thus, if these data were excluded, statistical significance would not be reached, since the resulting OR would be 1.05 [0.83–1.33].

When biochemical pregnancy rate was considered, a similar problem seemed to occur in reporting the data of the same author (Polyzos *et al.*, 2014). The meta-analysis (Chu *et al.*, 2018) considered 86 events in 129 vitamin D replete women and 210 in 368 'insufficient and deficient' women. However, the original work provided different data: 86/129 in vitamin D 'insufficient and replete' women and 124/239 in deficient women. We repeated the analysis, excluding these participants for not meeting the study criteria. The obtained OR was 1.02 [0.77–1.37], again being lower than reported by the authors, and without statistical significance.

When clinical pregnancy rates were analyzed, we observed some other discrepancies. The data from Polyzos were reported in the meta-analysis as follows: 70/129 in vitamin D replete women and 168/368 in 'insufficient and deficient women'. However, the original data are: 21/37 in replete women, 49/92 in insufficient and 98/239 in deficient participants, which makes 147/331 in 'insufficient and deficient' women instead of 168/368. In the same outcome, the data extracted from another author (Garbedian *et al.*, 2013) do not match with the original work. In the meta-analysis, it was reported that there were 66 events in 190 'insufficient and deficient' women instead of 33/95 women as given in the original work (Garbedian *et al.*, 2013). The obtained OR with the revised numbers is: OR 1.29 [1.06–1.55] which is somewhat lower than reported by the authors, but still statistically significant.

Finally, in the meta-analysis of the clinical pregnancy rates in autologous oocytes, Chu *et al.* (2018) provided the same confusion in the data for Polyzos *et al.* (2014), as shown in the previous paragraph.

According to our interpretation, in the aforementioned meta-analysis using the revised data, the replete vitamin D status only demonstrated to be significantly associated with the clinical pregnancy rates (OR 1.29 [1.06–1.55]), a significant but weak association. Regarding live birth rates (OR 1.05 [0.83–1.33]) and biochemical pregnancy rates (OR 1.02 [0.77–1.37]), a trend to better results was observed, but without reaching statistical significance.

Larger meta-analysis should be published in order to solve those questions.

Conflict of interest

None declared.

References

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Reply: Is the association of replete status in vitamin D with better results in IVF demonstrated?

Sir,

We thank Professor Matorras and team for identifying the discrepancies in our data extraction from the Polyzos *et al.* (2014) and Garbedian *et al.* (2013) primary articles.

We do not agree that the Polyzos *et al.* (2014) article should have been excluded from our review. Although this study had grouped the Vitamin D insufficient group in an unusual way, when compared with other studies, it was a well-conducted high-quality study that contained data directly relevant to our review question. Polyzos *et al.* (2014) scored very highly (score 9) on the Newcastle Ottawa Scale quality assessment tool. We believe exclusion of this study on the basis of unusual grouping will result in an incomplete summary of the available evidence. That said, we are now pleased to report that we have obtained primary data from Polyzos *et al.*, allowing us to categorize the data accurately. We have now updated our meta-analysis plots with correctly categorized data from Polyzos *et al.*, along with the corrected Garbedian *et al.*, data (Garbedian *et al.*, 2013) and append a new forest plot, which shows a meta-analysis of the studies reporting clinical pregnancy by vitamin D concentrations (Fig. 1). Our new forest plot continues to show that women who are vitamin D replete have a higher chance of achieving a clinical pregnancy (1.47 [1.04, 2.10]) from ART when compared with women with vitamin D deficiency or insufficiency. Supplementary figures are also provided for all other outcomes.

Given the lack of precision, shown by broad confidence intervals in our meta-analysis, we very much agree that further data from other groups conducting primary research are required and that future meta-analysis is required to interrogate the association between vitamin D levels and IVF treatment outcomes. As such, we are pleased to inform you that we have performed our own cohort study (data yet to be published), which further confirm the findings of our meta-analysis, strengthening our original conclusions.

Supplementary data

Supplementary data are available at *Human Reproduction* online.

Conflict of interest

None declared.

References

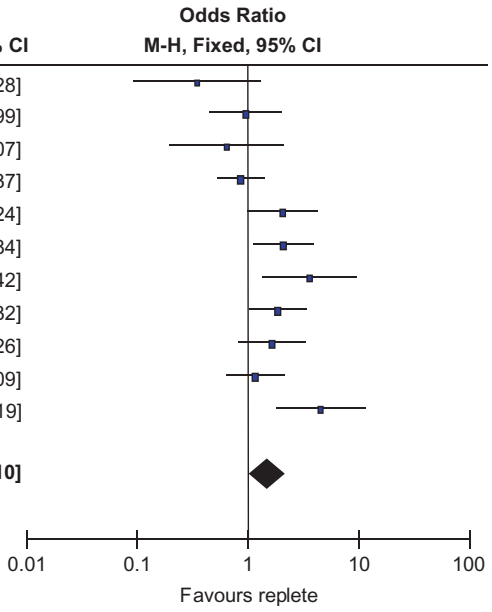
Garbedian K, Boggild M, Moody J, Liu KE. Effect of vitamin D status on clinical pregnancy rates following in vitro fertilization. *CMAJ Open* 2013;**1**: E77–E82.

Polyzos NP, Anckaert E, Guzman L, Schiettecatte J, Van Landuyt L, Camus M, Smitz J, Tournaye H. Vitamin D deficiency and pregnancy rates in women undergoing single embryo, blastocyst stage, transfer (SET) for IVF/ICSI. *Hum Reprod* 2014;**29**:2032–2040.

Study	Vit D replete Events	Total	Vit D deficiency/ insufficiency Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Anifanidis 2010	3	21	26	80	5.0%	0.35 [0.09, 1.28]
Fabris 2014	29	41	162	226	9.4%	0.95 [0.46, 1.99]
Firouzabadi 2014	4	16	70	205	5.8%	0.64 [0.20, 2.07]
Franasiak 2014	64	96	295	421	12.4%	0.85 [0.53, 1.37]
Fru 2014	37	58	30	65	9.5%	2.06 [1.00, 4.24]
Garbedian 2013	41	78	33	95	10.8%	2.08 [1.13, 3.84]
Ozkan 2008*	15	31	11	53	7.2%	3.58 [1.36, 9.42]
Paffoni 2014	23	64	63	271	11.1%	1.85 [1.03, 3.32]
Polyzos 2014	21	37	147	331	9.9%	1.64 [0.83, 3.26]
Rudick 2012	34	79	43	109	11.0%	1.16 [0.64, 2.09]
Rudick 2014	26	35	25	64	7.7%	4.51 [1.82, 11.19]
Total (95% CI)		**556**		**1920**	**100.0%**	**1.47 [1.04, 2.10]**
Total events	297		905			

Heterogeneity: Tau² = 0.20; Chi² = 25.43, df = 10 (P = 0.005); I² = 61%

Test for overall effect: Z = 2.16 (P = 0.03)



*Data extracted from figures within the manuscript

Figure 1 Meta-analysis of studies reporting clinical pregnancy by vitamin D concentrations. Meta-analysis of the data from all 11 included studies that reported clinical pregnancy as an outcome showed that women who are vitamin D replete have a higher chance of achieving a clinical pregnancy from ART when compared with women with vitamin D deficiency or insufficiency.

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